II. REMARKS

Formal Matters

Claims 1, 4-8, and 11-35 are pending and currently under examination in this application.

Claims 1, 4-8, and 11 were examined and were rejected.

Claims 1 and 5 are amended. No new matter is added by way of these amendments.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 4-8, and 11 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

As best understood by the Applicants, it is the position of the Office that the claims are not enabled because the instant specification has not shown *in vivo* working examples wherein subjects suffering from hyperlipidemia present reduced severity of symptoms after the administration of an antisense nucleic acid targeting apoE3. Applicants respectfully traverse the rejection.

To comply with 35 U.S.C. § 112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue."

Applicants respectfully submit that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, claims 1, 4-8, and 11 recite subject matter that is adequately described in the specification in such a way as to teach a skilled artisan how to make and use the claimed invention without having to practice undue experimentation.

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of

those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[1]

(1) the breadth of the claims

The instant claims recite administering an agent that reduces the amount of plasma active apoE in a host. The instant claims encompass the use of antisense nucleic acids that have the ability to effectively reduce expression of apoE, thereby reducing the amount of plasma active apoE, which in turn reduces VLDL production. In order to fall within a claim, an antisense nucleic acid must be able to reduce apoE expression. The number of "agents" encompassed by the claims is thus relatively small.

(2) the state of the art

As of the April 12, 1999 priority date of the instant application, the state of the art of making and using antisense nucleic acids to modulate gene expression was such that a person skilled in the art, given the nucleotide sequence of a given gene, could readily design, make, and use antisense nucleic acids that would reduce the expression of the gene.

The fact that design and use of antisense nucleic acids was a well-developed technology as of the April 12, 1999 priority date is supported by numerous publications in the field. These publications include publications which describe both the *in vitro* and *in vivo* use of antisense nucleic acids to modulate gene expression.

For example, the instant specification cites Wagner et al. ((1996) *Nature Biotechnol.* 14:840-844) which discusses potent and selective inhibition of gene expression by antisense heptanucleotides. Neurath et al. 1996 *Nat. Med.* 2(9): 998-1004, describes *in vivo* experiments in which the administration of p65 antisense phophorothioate oligonucleotides abrogates clinical and histological signs of colitis in a mouse model. In Morishita et al. 1994 *Gene* 149(1):13-19, researchers transferred antisense phosphorothioate oligos against cyclin B1- and CDC2 kinase-encoding genes into balloon-injured rat carotid artery as a potential therapy for experimental restenosis. Two weeks after transfection, antisense oligo treatment directed against either CDC2 kinase or cyclin B1 resulted in a partial, but significant, inhibition in neointima formation (Morishita et al. Abstract). The Neurath et al. and Morishita et al. references are included in an Information Disclosure Statement filed herewith. Numerous additional papers published before April 12, 1999 attest to the fact that design and use of antisense nucleic acids was a well-developed technology. Numerous textbooks published before April 12, 1999 further demonstrate the fact that the state of the art of antisense technology was highly developed. Such textbooks include, e.g.,:

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[1] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) Applied Antisense Oligonucleotide Technology (1998) C.A. Stein et al., Eds., Wiley-Liss;
2) Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors (1998) E. Wickstrom, Ed., CRC;
3) Antisense – From Technology to Therapy (1997) R. Schlingensiepen, Ed., Blackwell Science;
4) Antisense Oligodeoxynucleotides and Antisense RNA: Novel Pharmacological and Therapeutic Agents (1997) B. Weiss, Ed., CRC Press;
5) Delivery Strategies of Antisense Oligonucleotide Therapeutics (1995) S. Akhtar, Ed., CRC Press; and
6) Antisense Research and Applications (1993) S.T. Crooke and B. Lebleu, Eds., CRC.

Thus, as of the April 12, 1999 priority date, antisense technology was well developed and a variety of methods were available for the *in-vivo* administration of antisense oligonucleotides.

(3) the predictability or unpredictability of the art

In both the Final Office action and the Office Action dated May 23, 2006 the Office cites Mercola et al. ((1995) *Cancer Gene Therapy* 2:47-59; "Mercola"). The Office states that Mercola includes "cautionary remarks concerning the prospects of the antisense gene therapy." Office Action dated May 23, 2006, page 5.

The Office quotes Mercola as stating that "as with any therapeutic modality, problems arise, notable: (a) degradation of the oligomer…(b) inefficient cell uptake; (c) nonspecific binding; (d) nonspecific cleavage of mRNA …" The quoted statement from Mercola indicates that the cited problems are nothing more than would be expected to be faced with any therapeutic modality, and as such, are not indicative of problems unique to antisense technology.

Indeed, Mercola states:

> "Promising results make the considerable efforts of applying oligodeoxynucleotides in whole animals and in clinical trials more plausible. Conversely, oligodeoxynucleotide experiments which yield promising results in tissue culture can be generalized to the in vivo setting by development of clones of cells bearing plasmid-derived antisense RNA against the same target." Mercola, Abstract.

Mercola indicates that results in tissue culture can be generalized to *in vivo* results, and supports the fact that design and use of antisense nucleic acids was readily accomplished by the person of ordinary skill in the art. Thus, if anything, Mercola supports the fact that the instant claims are enabled.

(4) the quantity of experimentation necessary

In the Office Action dated May 23, 2006, the Office stated that Branch ((1998) *TIBS* 23:45-50) "notes the

importance of the time and expense necessary to screen large numbers of potential antisense molecules and to carefully monitor their *in vivo* effects, due to non-antisense effects and limits of specificity as well as accessibility of the antisense molecules." Office Action dated May 23, 2006, page 5.

However, the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[2]

As the court explained[3]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[4]

The instant claims recite use of an antisense nucleic acid that reduces the amount of plasma active apoE by reducing the expression of apoE. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which antisense nucleic acids retain the ability to reduce expression of apoE. Such antisense nucleic acids are determined through routine experimentation, typically employing nothing more than performing techniques that were routine in the art, as noted above. Since these experiments are routine in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires routine assays, no undue experimentation is necessary.

(5) the relative skill of those in the art

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and

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[2] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[3] *In re Wands* 8 USPQ 2d at 1404.
[4] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986).

reading of scientific journal articles. As such, the skill level of those designing and using antisense nucleic acids assays was high as of the April 12, 1999 priority date.

Furthermore, as noted above, the numerous papers and textbooks in the field of antisense technology attest to the fact that the skill level of those in the field of antisense technology was high as of the April 12, 1999 priority date.

(6) the amount of direction or guidance presented

The instant application provides data showing that overexpression and accumulation of apoE causes hypertriglyceridemia by stimulating VLDL production and by impairing VLDL lipolysis. It follows that reducing the plasma level of active apoE will also reduce the plasma level of VLDL.

Nucleotide sequences of apoE mRNAs were known as of the April 12, 1999 priority date of the instant application and available to the public. See, e.g., GenBank Accession No. M12529 – apoE mRNA sequence, published August 8, 1995; Breslow et al. (1982) *J. Biol. Chem.* 257:14639-14641 – human apoE cDNA sequence; and McLean et al. (1984) *J. Biol. Chem.* 259:6498-6504 – human apoE3 cDNA sequence. Those skilled in the art, given the known sequences of apoE genes, and given the advanced state of antisense technology, could have readily made and used antisense nucleic acids that would reduce apoE expression.

The Office asserts at page 3 of the current Office Action that "[p]ersons of ordinary skill in the art would reach a unanimous conclusion on the fact that in vivo clinical testing of any antisense nucleic acid is not routine in the art because clinical trials for new therapeutics, entail extensive, comprehensive, and thorough steps of evaluating the desired therapeutic effects in various groups of participating human subjects." The Office asserts further on page 4 of the current Office Action that "one might reasonably ask why there is only one antisense-based therapeutic agent (Vitravene) approved by the FDA to date since the discovery of antisense nucleic acids in 1978 . . . ."

Thus, the Office appears to suggest that successful human clinical trials and/or FDA approval would be necessary to enable the present claims. However, this is not the law. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), quoting *Scott v. Finney*, 34 F. 3d. 1058 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

(7) the presence or absence of working examples:

Compliance with the enablement requirement under 35 U.S.C. §112, first paragraph, does not require or

mandate that a specific example be disclosed. "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[5]

In sum, the amount of experimentation required to make and use an antisense nucleic acid that reduces expression of apoE would not be undue, and one of skill in the art would be able to perform the experiments as a matter of routine to determine the active nucleic acids.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1, 4-8, and 11 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

[5] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-121.

Respectfully submitted,
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